Regenerative Thymic Tissues as Curative Cell Therapy for Patients with 22q11 Deletion Syndrome

Grant Award Details

Regenerative Thymic Tissues as Curative Cell Therapy for Patients with 22q11 Deletion Syndrome

Grant Type: Quest - Discovery Stage Research Projects

Grant Number: DISC2-11109

Investigator:

Name:	Vittorio Sebastiano
Institution:	Stanford University
Type:	PI

Disease Focus: Immune Disease, Thymic Disorder, 22q11 Deletion/DiGeorge

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $865,282

Status: Pre-Active

Grant Application Details

Application Title: Regenerative Thymic Tissues as Curative Cell Therapy for Patients with 22q11 Deletion Syndrome

Public Abstract:

Research Objective

We propose a platform to generate transplantable thymus organoids derived from human pluripotent stem cells designed to treat severe immunodeficiencies in children affected by 22q11 DS

Impact

Our product could impact 22q11DS and many other pathologies characterized by absence, degeneration or injury of the thymus and resulting in severe immunodeficiencies.

Major Proposed Activities

- Implementation and optimization of conditions that lead to robust, pure, and efficient formation of Thymic Epithelial Cells in 2D from human pluripotent stem cells, exploring signaling pathways.
- Identify biomatrices and culture conditions to promote 3D thymus organoid formation, and test maturation of gene expression of functional thymus markers like FOXN1, Delta-like Notch ligands, AIRE.
- Characterize at the molecular level in vitro derived TECs in comparison to fetal thymic tissues by RNASeq and ATASeq to study transcriptional regulation and chromatin openness and organization.
- Defining and Correcting the Cell-Intrinsic Defects in 22q11 TEC Ontogeny and identify potential drugs/pathways (e.g. Vitamin B12, retinoid acid) that could compensate for the thymic defects in 22q11DS
- Test transplantability and efficacy of thymic organids in vivo in nude athymic mice and assess T-cell maturation and reconstitution of TCR repertoire upon cotransplantation of hematopoietic stem cells
- Understanding Sustainability and Structural Organization of the Thymic Organoid In Vivo by assessment of growth, compartmentalization, maturation, and vascularization of the transplants

Statement of Benefit to California:

Our objective is to develop a therapeutic product designed to treat children with 22q11DS and severe immunodeficiency (complete DiGeorge) with no access to allogenic thymic transplantation and urgent need for alternative therapies. These children, if not treated, have a life expectation of just two years. Our research will benefit the state of California and its citizens by significantly advancing the medical therapy and options for the community.

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